REMARKS

Claims 134, 139-143, 145 and 148-155 and 157-175 are now pending in this application. Favorable reconsideration is respectfully requested.

The rejection of the claims under 35 U.S.C. §112, second paragraph, is believed to be obviated by the amendments submitted above. Claim 134 is believed to have been appropriately amended. Claims 143 and 166 have been amended to delete the phrase "which anchors said C-terminal fragment to a membrane of a eukaryotic cell expressing a MSP-1 protein."

In view of the foregoing, the claims are definite within the meaning of 35 U.S.C. §112, second paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 153, 156, 159, 162, 165, 169, 172 and 175 under 35 U.S.C. §103(a) over Longacre in view of Longacre et al. is respectfully traversed. Those references fail to suggest the claimed composition.

Claim 153 is directed to a recombinant protein whose polypeptide sequence consisting essentially of:

a) a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met1 to Asp32; and

b) a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium cynomolgi* from Lys276 to Ser380 as shown in SEQ ID NO: 11 which fragment induces an immune response which can inhibit parasitemia in vivo in a host infected with a *Plasmodium* parasite, and wherein the fragment has atomic coordinates in Annex I; and NMR fingerprints of Figures 12.0a to 12.0c.

Longacre describes the C-terminal sequence of *Plasmodium cynomolgi* merozoite surface protein 1 and its homology with other *Plasmodium* species. This reference fails to disclose a leader sequence comprising thirty-two amino acids of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium vivax* from Met1 to Asp32. This reference also fails to disclose or even suggest a MSP-1 protein with the atomic coordinates and fingerprints as recited in Claim 153. Longacre also fails to describe the use of the frgamnet Lys276 to Ser380 as shown in SEQ ID NO: 11. There is no suggestion in Longacre which fragment induces an immune response which can inhibit parasitemia in vivo in a host infected with a *Plasmodium* parasite.

Longacre et al. disclose *Plasmodium vivax* merozite surface protein 1 recombinant proteins, which were produced in baculovirus. These proteins include the 19 kilodalton C-terminal fragment of MSP-1 protein from *Plasmodium vivax*.

The combination of Longacre and Longacre et al. fails to suggest the recombinant protein of Claim 153. Neither reference suggests the use of a 19 kilodalton C-terminal fragment of a surface protein 1 of a merozoite form (a MSP-1 protein) of *Plasmodium cynomolgi* from Lys276 to Ser380 as shown in SEQ ID NO: 11, which induces an immune response which can inhibit parasitemia in vivo in a host infected with a *Plasmodium* parasite.

In view of the foregoing, Claim 153 and claims dependent thereon are not obvious over Longacre and Longacre et al. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Longacre in view of Longacre et al. and further in view of Holder et al. is respectfully traversed. These references fail to suggest the claimed composition.

Neither Longacre nor Longacre et al. disclose that alum can be used successfully as an adjuvant in combination with recombinant C-terminal MSP-1 19 C-terminal fragment from a *Plasmodium* parasite.

Holder et al. disclose EGT-like domains from the MSP-1 protein. Although this reference mentions that these sequences can be used as vaccines and can be administered with an appropriate adjuvant such as alum, all of the examples illustrating some protective immune response of the EGT-like proteins used Freund's complete or incomplete adjuvant.

It was not predictable whether the adjuvant of alum in combination with recombinant C-terminal MSP-1 19 C-terminal fragment from *Plasmodium* parasite could achieve any immune response. Holder et al. fail to demonstrate that alum could be achieved any immune response. Holder et al. fail to demonstrate that alum could be used as an adjuvant in combination with EGF-like domains and an immune response was achieved.

In view of the fact that Holder et al. does not show any immune response using the EGF-like domains with alum, Applicants submit that a skilled artisan would not have any expectation of success that a 19 kilodalton C-terminal fragment of an MSP-1 protein of a *Plasmodium* parasite and alum can be effective in a vaccinating composition. This is because there was at the time of filing of the present application an unpredictability in the malaria art of whether an immune response could be achieved using certain adjuvants, other than Freunds adjuvant, in conjunction with recombinant malaria constructs.

Thus, without such expectation of success the presently claimed invention should not be rendered obvious, since there must be a reasonable expectation of success coupled with a suggestion in the art in order for an invention to be deemed obvious. See In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Moreover, Holder et al. fail to disclose that alum when used in conjunction with a C-terminal MSP-1 protein, more specifically EGF-1 or EGF-2, has a better immune response than Freunds, as demonstrated in the present invention. See Figure 10A and 10B of the specification which show that less parasitemia was observed in squirrel monkeys immunized with MSp-1 p19 and alum than with MSP-1 p19 and Freunds. This unexpected result is neither demonstrated nor suggested in Holder et al.

Since Holder et al. is silent with respect to a diminution of parasitemia when alum is used as an adjuvant in comparison with Freunds, Applicants submit that the combination of references fails to render obvious the presently claimed invention to the skilled artisan. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Chappel et al., Miller et al., Longacre et al. and Longacre is respectfully traversed. These references fail to suggest the claimed composition.

It will be demonstrated below that none of these references alone or in combination teach or suggest modifying the specific constructs to achieve those of Claims 151 and 152 and those claims dependent thereon. Furthermore, there is absolutely no teaching or even suggestion of the oligomer claims of Claims 167, 168, 170, 171 or 173.

Chappel et al. disclose monocional antibodies that inhibit *Plasmodium falciparum* invasion *in vitro* and recognize the first growth-factors-like domain of the merozoite surface protein 1.

It appears that the Examiner focuses on the three recombinant constructs described in Chappel et al. Two of these constructs contain the MSP1EGF1 and MSP1EGF2 regions fused to glutathione S-transferase. These two recombinant proteins are fusion proteins, which have nothing in common with the claims set forth in the present rejection. Also the sequences from MSP1 are shorter sequences containing a nucleic acid sequence encoding 47 and 52 amino acids respectively from MSP1EGF1 and MSP1EGF2.

The third recombinant construct is an insect cell product, S42ΔA contains a nucleic acid sequence encoding 271 amino acids from the Wellcome strain of MSP1, including both EGF-like domains fused to nucleic acid sequence encoding 34 amino acids of MSP1 to provide a signal for secretion.

None of these constructs recites a recombinant protein comprising a leader sequence from *Plasmodium vivax* having a nucleic acid sequence encoding 32 amino acids and a 19 kilodalton C-terminal MSP-1 fragment from *Plasmodium falciparum* containing a nucleic acid sequence encoding 92 amino acid sequences (Claim 151) or 113 amino acid sequences (Claim 153) as claimed.

Moreover, there is no suggestion to those skilled in the art to modify any of these constructs. Furthermore, Chappel et al. do not demonstrate or clearly suggest that these constructs set forth therein can inhibit parasitemia *in vivo* with a host infected with a *Plasmodium* parasite, as recited in the claims and is silent with respect to the claimed oligomers.

Miller et al. was cited to confirm the numbering of the S42ΔA construct described in Chappel et al. The fact that the Examiner has cited this reference and has focused on the specific S42ΔA construct is a clear indication that the Examiner is using hindsight in this rejection. Of course, hindsight is not acceptable in making a rejection under 35 U.S.C. §103(a).

Longacre et al. disclose *Plasmodium vivax* MSP-1 C-terminal recombinant proteins produced in baculovirus. These recombinant constructs have a leader sequence of 35 bp and contain a nucleic acid sequence encoding 401 amino acids or 124 amino acids (anchored form) and 379 amino acids or 102 amino acids (secreted form). Moreover, Longacre et al. fail to demonstrate that their constructs can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite, as recited in the claims. Moreover, there is no disclosure of oligomers as set forth in Claims 167, 168, 170, 171 and 173.

Longacre described *Plasmodium cynomolgi* MSP-1 C-terminal sequence and its homologies with other *Plasmodium* species. There is no demonstration in this reference that any of these disclosed sequences can achieve inhibition of parasitemia *in vivo* in a host infected with a *Plasmodium* parasite. There is also no disclosure of oligomers, as presently claimed.

In the Official Action dated August 24, 2004, the Examiner states that it would have been well within the skilled artisan to substitute the *P. vivax* signal and anchoring sequences of the homologous sequences of *P. falciparum* and as such the immunological function of *P. falciparum* would not have been influenced. However, as taught in Longacre et al., there is no cross-reactive immunity between *P. vivax* baculovirus recombinants and those of *P. falciparum*. This is evidenced at least on page 203 of Longacre et al., which states:

> Since the baculovirus recombinants from this region appear to retain many conformational epitopes of the native protein, the question of cross reactivity between P. vivax and P. falciparum MSP1 molecules could be addressed. We were unable to demonstrate any cross reactivity of our baculovirus recombinant protein by immunoblot under non reducing conditions with either polyclonal rabbit antisera against affinity purified P. falciparum MSP1 [45] or monoclonal antibodies 1114.4 and 111.5 directed against C-terminal conformation epitopes [7].

Therefore, one skilled in the art would not definitely consider substituting *P. vivax* with *P. falciparum* and expect to achieve the same immunological function.

Finally, the combination of these references fails to render the presently claimed invention obvious since none of these references demonstrate that the recombinant constructs can achieve inhibition of parasitemia in vivo in a host inflicted with a *Plasmodium* parasite. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. §103(a) over Chappel et al., Miller et al., Longacre et al., Longacre, and further in view of Holder et al. is respectfully traversed. These references fail to suggest the claimed composition.

Chappel et al., Miller et al., Longacre and Longacre et al. are discussed above. Applicants submit that the conclusion that can be reached in the combination of these references is that one skilled in the art would not be persuaded to substitute similar recombinant constructions for *P. vivax* with *P. falciparum* and expect to maintain the same immunological function. This is especially in view of the fact that the monoclonal antibodies 111.2 and 111.4 described in Chappel et al. did not cross react with the baculovirus produced *P. vivax* constructs described in Longacre et al.

As discussed above, Holder et al. fail to disclose that alum when used in conjunction with a C-terminal MSP-1 protein, more specifically EGF-1 or EGF-2, has a better immune response than with Freunds. This is demonstrated in Figure 10A and 10B in the specification wherein less parasitemia was observed in squirrel monkeys immunized with MSP-1 p19 and alum than with MSP-1 p19 and Freunds. This unexpected result is neither demonstrated nor contemplated in Holder et al.

Thus, Applicants submit that the combination of these references lack the necessary criteria to render the presently claimed invention obvious. Withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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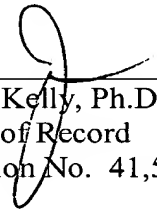

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